Cancer's Other Half: Limiting Metastasis by Restricting Blood Vessel Formation

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Cancer has two halves: malignant cells that initiate oncogenesis, and cancer stromal cells that form the tumor microenvironment. Isocitrate dehydrogenases (IDHs) are enzymes in normal cellular metabolism. Cells with IDH mutations produce 2-hydroxyglutarate (2HG), and 2HG directly transforms normal cells to malignant cells through histone demethylation. However, whether IDH mutations affect cancer stromal cells is elusive. I hypothesized that the IDH-mutant cancer secretome would stimulate oncogenic vascular genesis. First, I isolated IDH-mutant fibrosarcoma secretome and treated vascular-endothelial cells. The IDH-mutant cancer secretome stimulated vascular tube formation by ~138% relative to control, by quantitative NIH/Image J analysis and statistical comparisons, suggesting that IDH-mutant tumors may metastasize by stimulating angiogenesis. Then, I followed up with an additional question of whether GSK864, a small-molecule allosteric IDH inhibitor, would attenuate vascular genesis. Remarkably, GSK864 attenuated vascular formation by ~36%, relative to the control, suggesting a potential to reduce metastasis of IDH-mutant cancers. Furthermore, I asked another question of whether 2HG, an IDH-mutant oncometabolite, would specifically stimulate angiogenesis. Indeed, 2HG not only reversed GSK864 attenuation, but also significantly stimulated vascular genesis in the GSK864-treated cancer secretome. Finally, I performed yet another experiment, and found that exogenous 2HG alone stimulated vascular genesis, identifying 2HG as a key culprit of oncogenesis angiogenesis and thus a therapeutic target. These findings suggest novel mechanisms by which the IDH-mutant cancer secretome and/or metabolite, specifically 2HG, induces oncogenic angiogenesis and metastasis.

Awards Won:

Third Award of $1,000